REMARKS

Personal Interview

Applicants would like to express their appreciation for the courtesy extended by the Examiner to Applicants' agent, Angela Dallas Sebor, in the personal interview on April 19, 2005. During the interview, Dr. Sebor discussed the rejection under 35 U.S.C. § 103, and particularly the arguments presented in the last written response regarding the cited combination and specifically, the Lobb et al., Wigzell et al., Schramm et al., and Krause et al. references. With regard to Lobb et al., Dr. Sebor discussed the data in Fig. 4 of Lobb et al. showing that anti-VLA4 actually increased the lymphocyte numbers in the lungs of the animal, and further argued that there is no motivation to combine this reference with the other references. With regard to Schramm et al., Dr. Sebor and Examiner Schwadron discussed the fact that Schramm et al. teaches a complete systemic depletion of the lymphocytes, which is not consistent with a therapeutic strategy, as argued by Dr. Sebor, whereas the claimed invention provides a therapeutic benefit in the absence of systemic depletion of the T cell subset. The Examiner agreed that this is an important point of distinction over the cited art and suggested that the claims be amended to reflect this point. Dr. Sebor agreed to consider the presentation of such amended claims.

Claim Amendments

Claim 1 has been amended to adopt the Examiner's suggestion that the claim recite that the method inhibits airway hyperresponsiveness without substantially affecting peripheral T cell responses. Support for the particular amendment to Claim 1 is found in the specification on page 10, lines 10-18, and in Example 5. Support for the amendment to Claim 33 is found in the specification on page 10, lines 22-28, page 34, lines 9-25, and Example 1.

Rejection of Claims 1, 2 and 9-35 Under 35 U.S.C. § 103:

The Examiner has maintained the rejection of Claims 1, 2 and 9-35 under 35 U.S.C. § 103, contending that these claims are not patentable over Lobb et al. (U.S. Patent No. 5,871,734) as evidenced by Arrhenius et al. (U.S. Patent No. 5,869,448), in view of Schramm et al., Wigzell et al.

(U.S. Patent No. 5,958,410), and Krause et al. (USPAP 2002/0037286). In addition to reiterating the prior reasons for the rejection, the Examiner responds to Applicants' last reply by contending that Lobb et al. teach aerosol administration of an antibody which binds T cells to treat asthma and Schramm et al. teach that a different antibody which binds T cells can be used to treat asthma. The Examiner further quotes a section of Lobb et al. (col. 8, last paragraph) regarding inhibition of leukocyte recruitment to VCAM-1 expressing epithelium, apparently in support of the contention that Lobb et al. teach inhibition of T cells to treat asthma. With regard to Schramm et al., the Examiner asserts that Schramm et al. teach that animals have asthma, receive the anti-TCR antibody, and the asthma is resolved, and further contends that there is no teaching in Schramm et al. that a complete systemic depletion of an entire T cell subset is required in the antibody treated animals. The Examiner contends that there is no evidence that any of the secondary references lack enablement. Finally, the Examiner submits that given that the anti-VLA4 antibody of Lobb et al. binds T cells and that anti-TCR of Schramm et al. can be used to treat asthma, it is reasonable to conclude that the method of Lobb et al. using aerosol administration can be practiced using the antibody of Schramm et al.

Applicants again traverse the Examiner's rejection of Claims 1, 2 and 9-35 under 35 U.S.C. § 103, and again submit that the combination of references particularly fail to provide the requisite motivation to combine the references to arrive at the claimed invention and further, fail to provide a reasonable expectation of success to arrive at the claimed invention. Moreover, Applicants submit that the combination of references fails to teach or suggest an *aerosolized antibody* having one of the particularly recited receptor specificities, *wherein the binding of the antibody to the receptor causes the depletion or inactivation of the T cell.*

Initially, however, Applicants note that the claims have been amended in the manner suggested by the Examiner in the April 19 interview. This amendment emphasizes an important feature of the present invention, which the Examiner suggested would be useful in clarifying the distinctions of the present invention over the cited art. Specifically, Claim 1 has been amended to recite that the method is effective in the absence of a substantial effect on peripheral T cell responses.

With regard to the rejection, as discussed with the Examiner in the April 19 interview, for the Examiner to include Lobb et al. in the combination, the Examiner has taken the position that anti-VLA4 binds to T cells, and therefore, since asthma is inhibited in animals to which the antibody is administered, the result must be via an action on T cells commensurate with what is claimed (*e.g.*, by depletion or inactivation of T cells). However, Applicants submit that there is absolutely no teaching or even a suggestion in Lobb et al. that the effects of the anti-VLA4 on asthma, *regardless* of whether the antibody can bind to T cells, resulted from any action on T cells. Indeed, the data of Lobb et al. show that not only did anti-VLA4 *not have an effect* on lymphocyte numbers or recruitment, it appears as though anti-VLA4 may have actually *increased* the lymphocytes in the lungs of the animal (Fig. 4B of Lobb et al.). Lobb et al. provide no other relevant discussion of lymphocytes and no specific mention of T lymphocytes at all in the patent. However, Lobb et al. provide a *clear teaching* that anti-VLA4 administration caused a significant inhibition of the recruitment of neutrophils and eosinophils to the lung (column 3, lines 4-7 and column 12, lines 10-21), which are the only leukocytes that Lobb et al. appear to attribute the inhibition of the asthma responses.

Therefore, Lobb et al. simply do not teach or suggest an aerosolized antibody that binds to a T cell receptor and causes the depletion or inactivation of the T cell, nor the modulation of T cells to treat asthma, nor would the teachings of Lobb et al. motivate one of skill in the art to look at the modulation of T cells to treat asthma or airway hyperresponsiveness. At best, the teachings of Lobb et al. would suggest that one might look at methods of targeting *eosinophils or neutrophils* to treat asthma, and could further suggest that modulation of T cells is not necessary, or is not effective using an anti-VLA4 antibody. This is a *teaching away* from the present invention. Therefore, one of skill in the art would simply not find any motivation or expectation of success provided by Lobb et al. to look to any of the other references in the Examiner's combination.

With regard to the combination of Lobb et al. with Schramm et al., and further with Wigzell et al. and Krause et al., it should be clear that Lobb et al. do not teach or suggest the method of the present invention, and in fact, provide absolutely no motivation or expectation of success at targeting

a T cell to treat asthma, and the other references in the combination do not remedy this deficiency or provide any suggestion or motivation to be combined with Lobb et al.

In particular, Schramm et al. is a research study showing that *complete, systemic depletion* of an entire T cell subset ($\alpha\beta$ or $\gamma\delta$) from an animal, either by genetic manipulation or by intravenous antibody administration, prevents the development of airway inflammation and bronchial hyperactivity in mice. The Examiner submits that Schramm et al. do not teach that a complete systemic depletion of an entire T cell subset is required in the antibody treated animals. However, Applicants submit that Schramm et al. do not teach anything except depletion of the animals - Schramm et al. clearly teach that the antibody treatment was to deplete the animals of a subset of T cells (page 220, col. 2, first sentence of last paragraph: "[s]imilar findings were observed in mice **depleted** of TCR$\gamma\delta$ or TCR$\alpha\beta$ cells by treatment with monoclonal antibodies" (emphasis added). The study is primarily directed to determining the role of $\gamma\delta$ T cells in asthma, and also to dissect the roles of the two T cell subsets. Schramm et al. do not teach or suggest *the therapeutic use* of any antibodies for the treatment of asthma. As previously submitted, complete, systemic depletion of T cells would *not* be viewed by one of skill in the art as a therapeutic approach to treatment of a disease, including airway inflammation and/or hyperresponsiveness, because of course complete, systemic depletion of a major arm of the immune system as a therapy would have undesirable consequences for the animal. Moreover, Schramm et al. do not teach or suggest the use of aerosolized antibodies or the administration of antibodies to the lung of an animal. One does not learn from the teachings of Schramm et al. that one could or should therapeutically deplete or inactivate the pulmonary T cells in an animal to treat airway hyperresponsiveness in the animal, and moreover, one can not learn from the teachings of Schramm et al. that one can deplete pulmonary T cells and treat airway hyperresponsiveness without substantially effecting peripheral T cells in the animal. It is believed that the Examiner acknowledged this point in the April 18 interview. Thus, there is no suggestion, motivation or expectation of success provided by Schramm et al. to make or use the present invention, even when combined with the other references. There is absolutely no motivation or suggestion in any of the references in the cited combination to move the antibody of

Schramm et al. into *any* therapeutic method, let alone the method of Lobb et al., which only suggests targeting eosinophils or neutrophils via blocking of an adhesion molecule.

As discussed in prior responses, Wigzell et al. and Krause, even when combined with Lobb et al. and Schramm et al., do not remedy the above-described deficiencies, for the reasons of record.

In summary, in view of the discussion above, the combination of references fails to teach or suggest the use of aerosolized antibody that binds to and depletes or inactivates the recited T cells receptors, whereby aerosolized administration of said antibodies reduces airway hyperresponsiveness in a mammal. Moreover, the combination fails to provide any motivation to make the combination as the Examiner has done, or to motivate one to make and use the present invention. Finally, the combination does not provide any expectation of success at making and using the present invention. Therefore, the Examiner has not established a *prima facie* case of obviousness in view of the combination of references.

In addition, Applicants again submit that the present invention provides advantages over the art at the time of the invention, including the ability to target pulmonary T cell populations in the absence of any substantial effect on peripheral T cells, and the efficacy of the method at extremely *low* doses of antibody. The advantages of the invention only further separate the claimed invention from the art.

In view of the foregoing remarks, Applicants respectfully request that the Examiner withdraw the rejection of Claims 1, 2 and 9-35 under 35 U.S.C. § 103.

Applicants have attempted to respond to the Examiner's rejections as set forth in the February 14 Office Action, and submit that the claims are in a condition for allowance. In the event that the Examiner has any remaining concerns regarding Applicants' position, he is encouraged to contact the below-named agent at (303) 863-9700 to expedite the allowance of this application.

Respectfully submitted,

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